Antithrombotic

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Under Supervision
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Done by Group A
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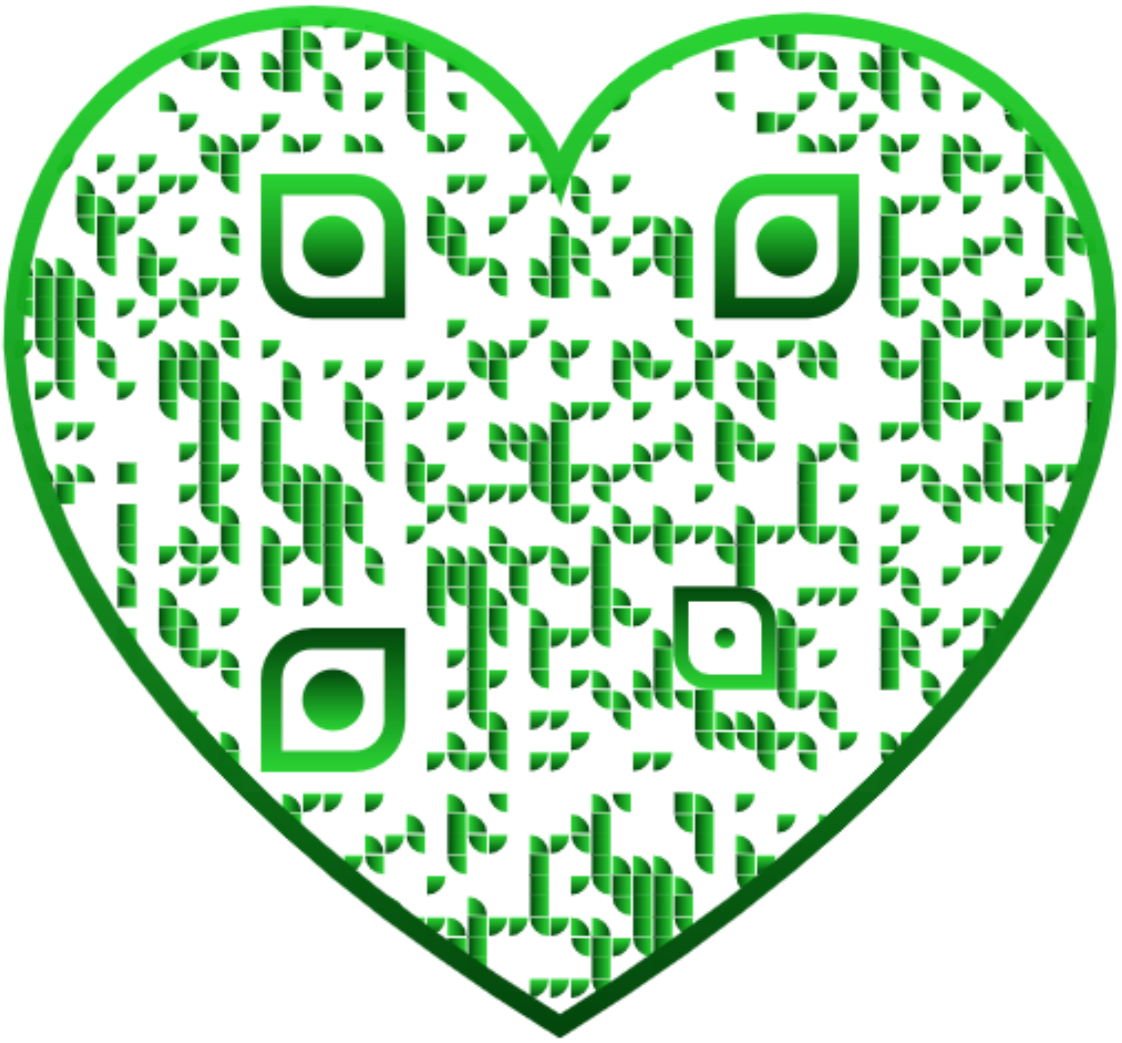
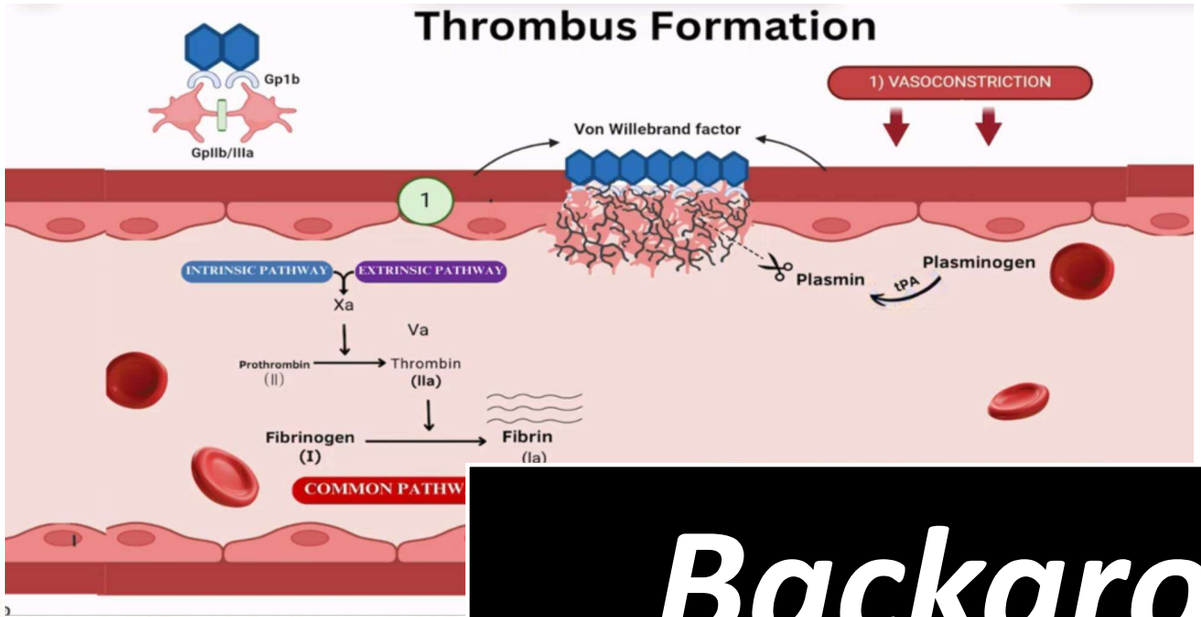
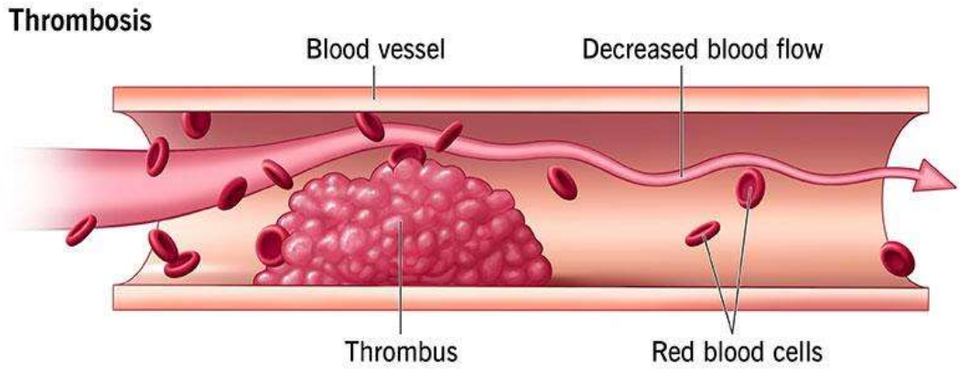


LEARNING OBJECTIVES

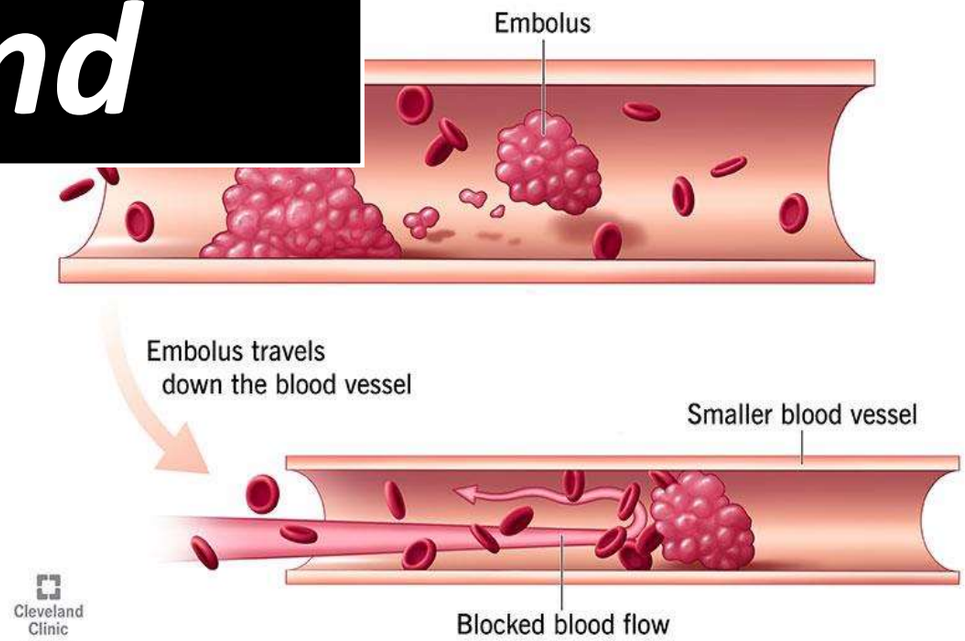
- Understand the mechanisms of thrombus formation and the principles of hemostatic balance.
- Classify various antithrombotic agents, including antiplatelets, anticoagulants, and fibrinolytics.
- Master the administration protocols and monitoring requirements for key medications such as Heparin and Warfarin.
- Identify clinical indications and guideline-based recommendations for managing Venous Thromboembolism (VTE), Atrial Fibrillation (AF), Acute Coronary Syndrome (ACS), and Ischemic stroke.


Thrombus Formation
Gp1b
GpIIb/IIIa
1) VASOCONSTRICTION
Von Willebrand factor
1
INTRINSIC PATHWAY
EXTRINSIC PATHWAY
Xa
Va
Prothrombin
(II)
Thrombin
(IIa)
Fibrinogen
(I)
Fibrin
(Ia)
Plasmin
tPA
Plasminogen
COMMON PATHW

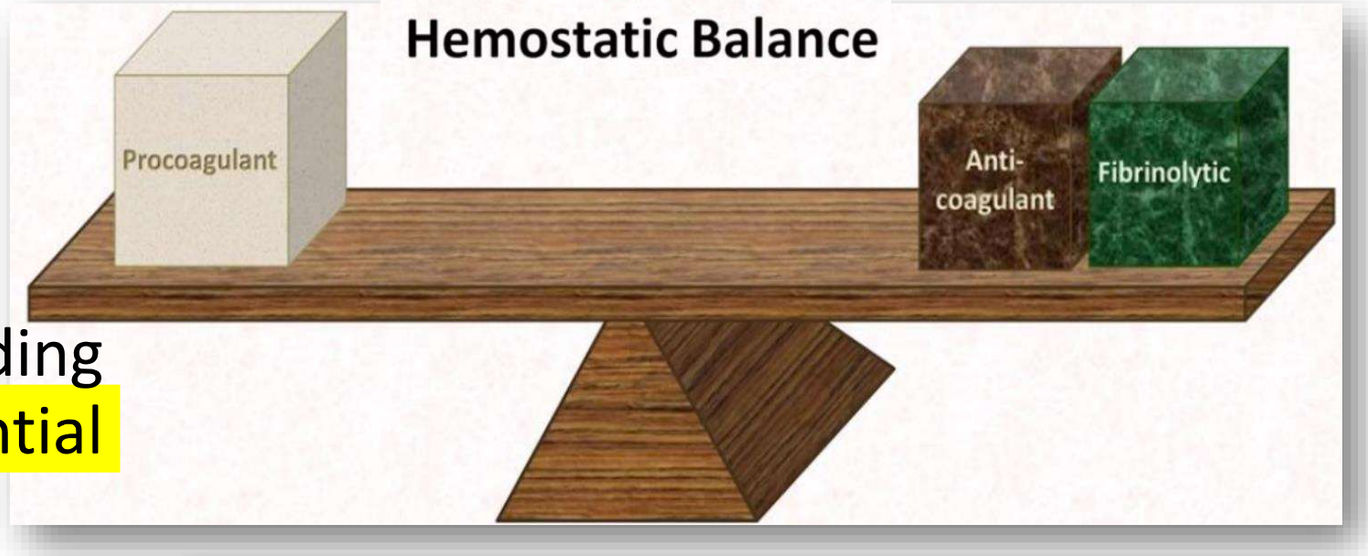

Thrombosis
Blood vessel
Decreased blood flow
Thrombus
Red blood cells

Background

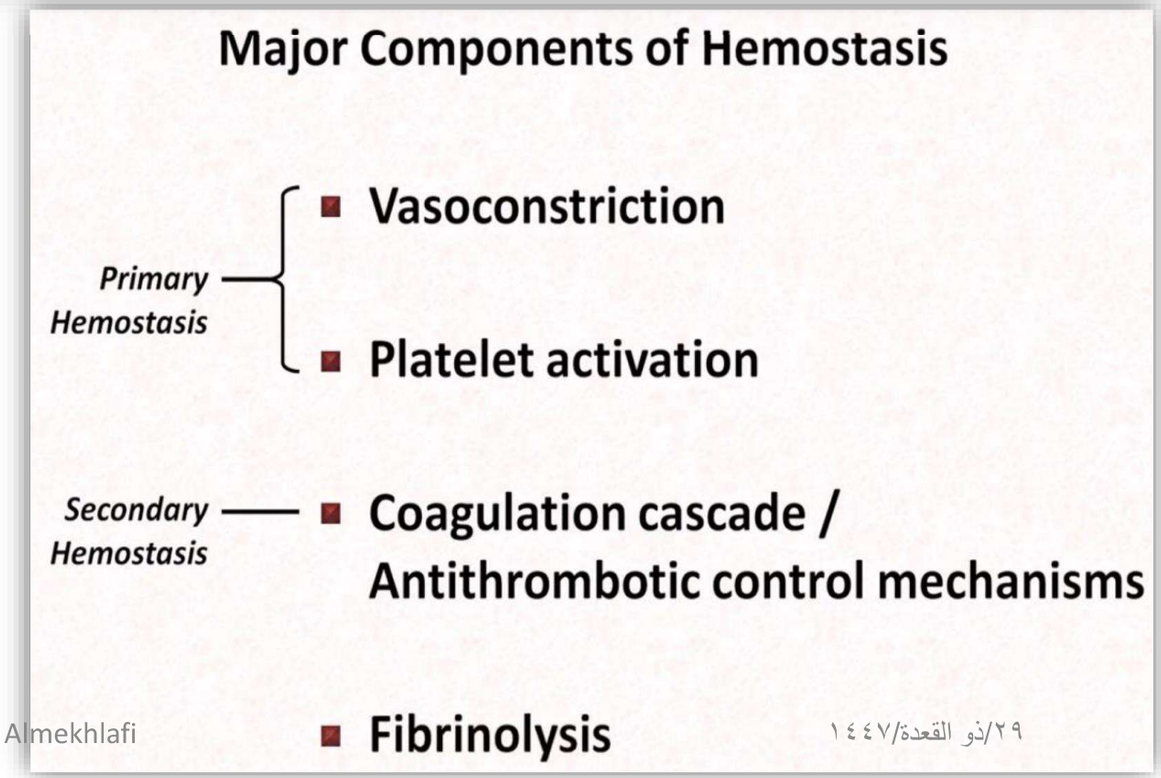
Procoagulant
Anti-
coagulant
Fibrinolytic

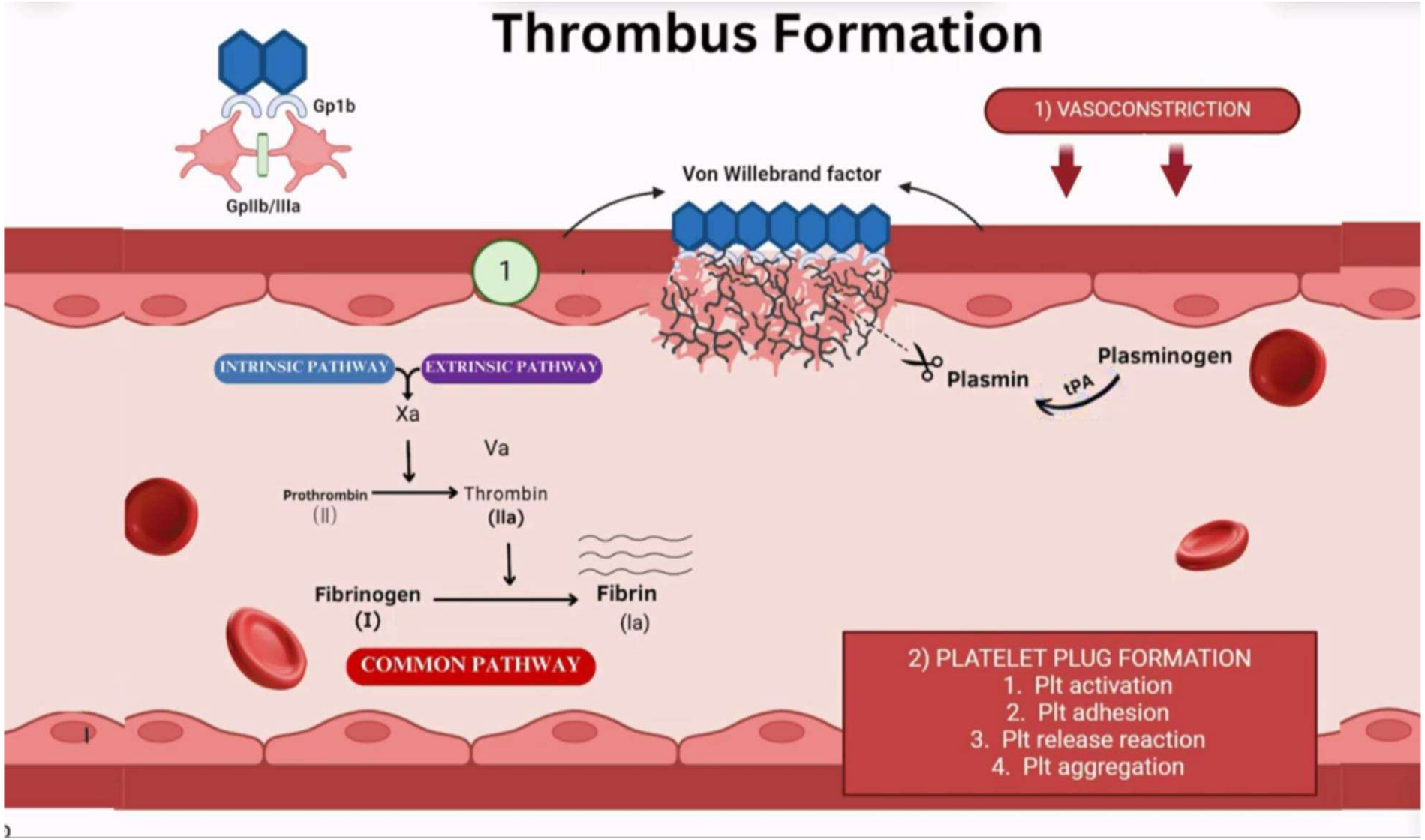

Embolus
Embolus travels
down the blood vessel
Smaller blood vessel
Blocked blood flow
Cleveland
Clinic
©2021

Hemostasis



- **Hemostasis:** the arrest of bleeding following vascular injury, is essential to life.
- There is a balance that prevent thrombosis and hemorrhage.
- When a vessel is injured, a dynamic interplay between **thrombogenic (activating)** and **antithrombotic (inhibiting)** forces results in the local formation of a hemostatic plug that seals the vessel wall and prevents further blood loss.




Thrombus Formation
Gp1b
GpIIb/IIIa
1) VASOCONSTRICTION
Von Willebrand factor
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INTRINSIC PATHWAY
EXTRINSIC PATHWAY
Xa
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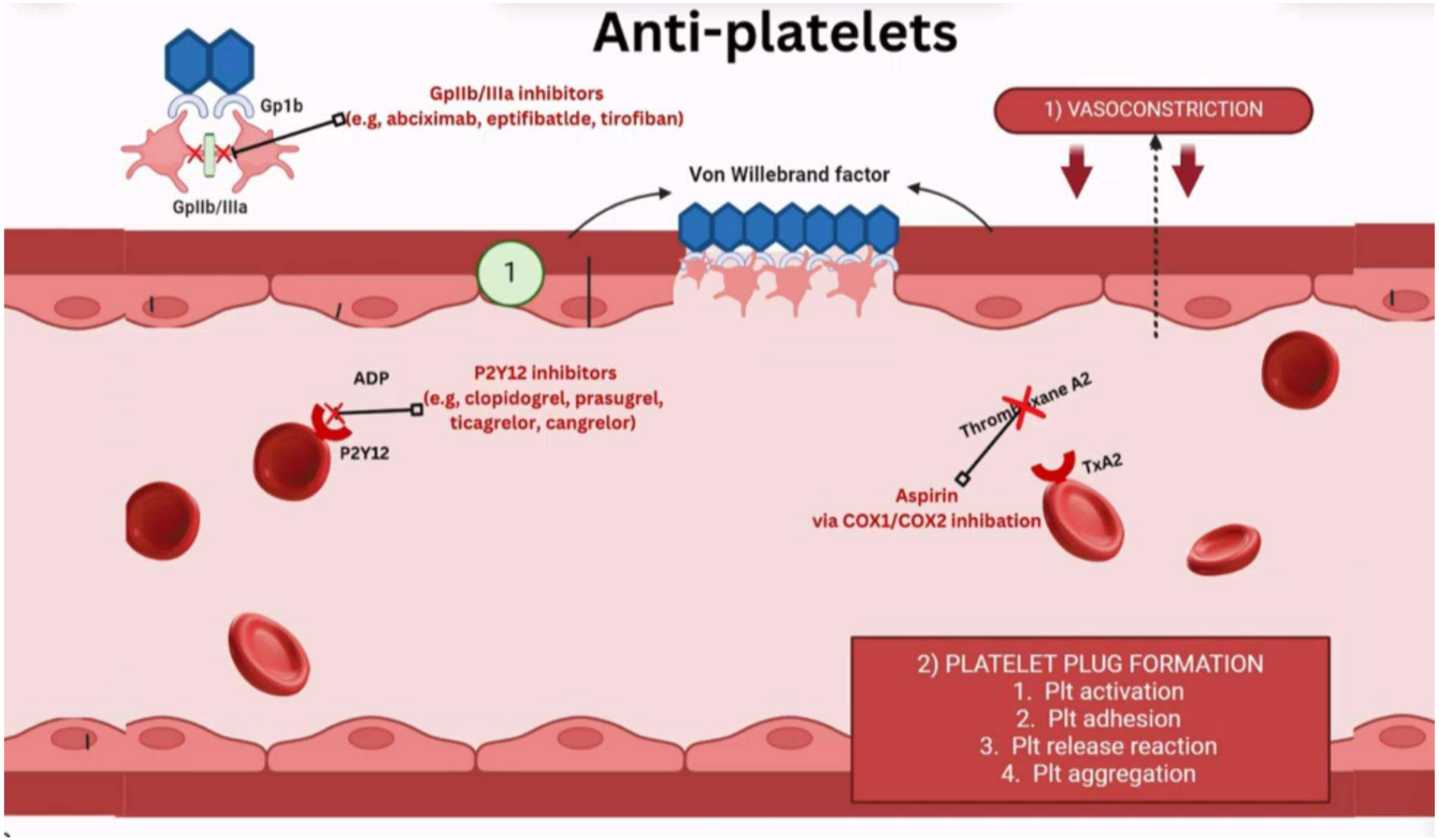
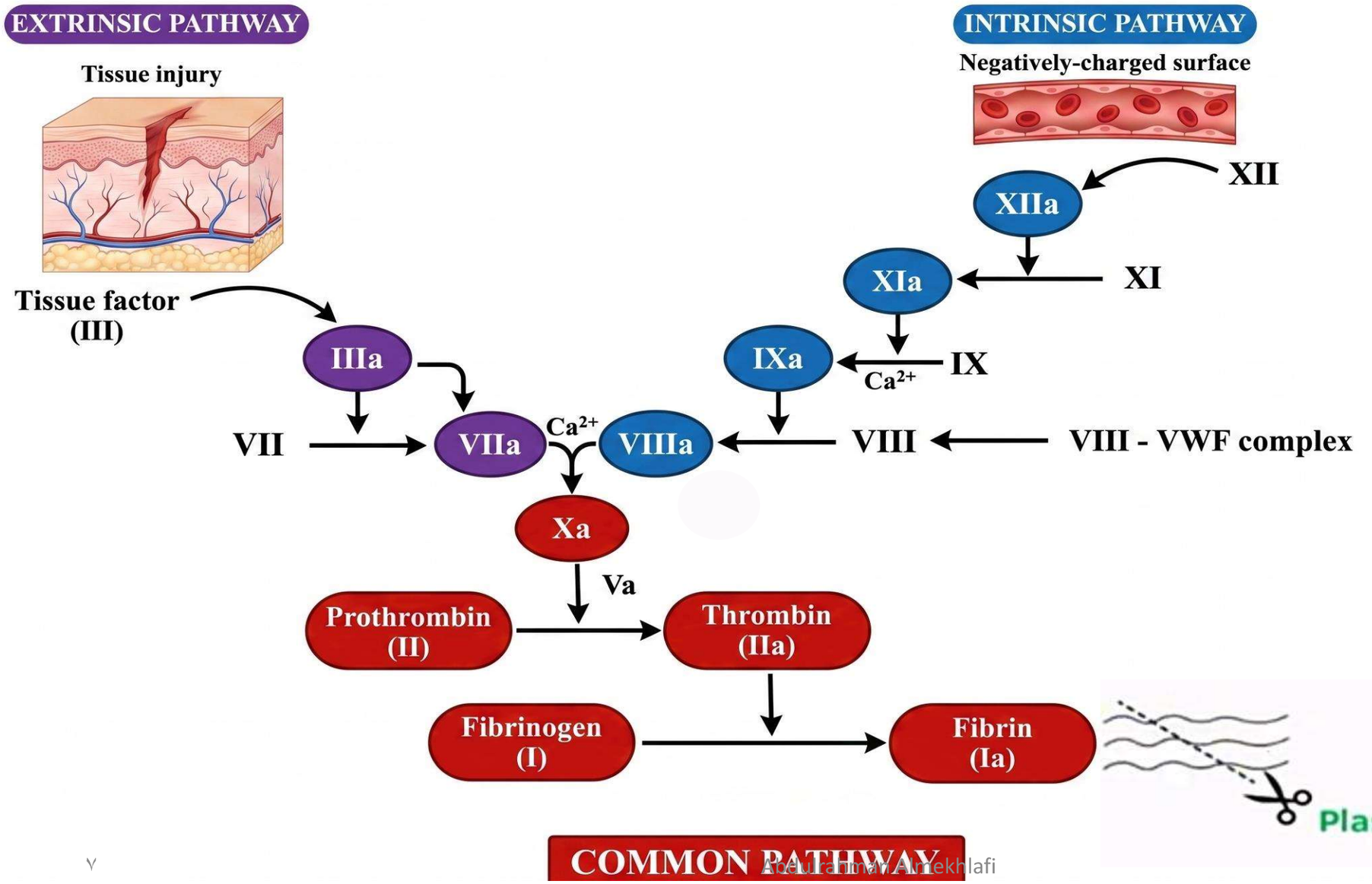
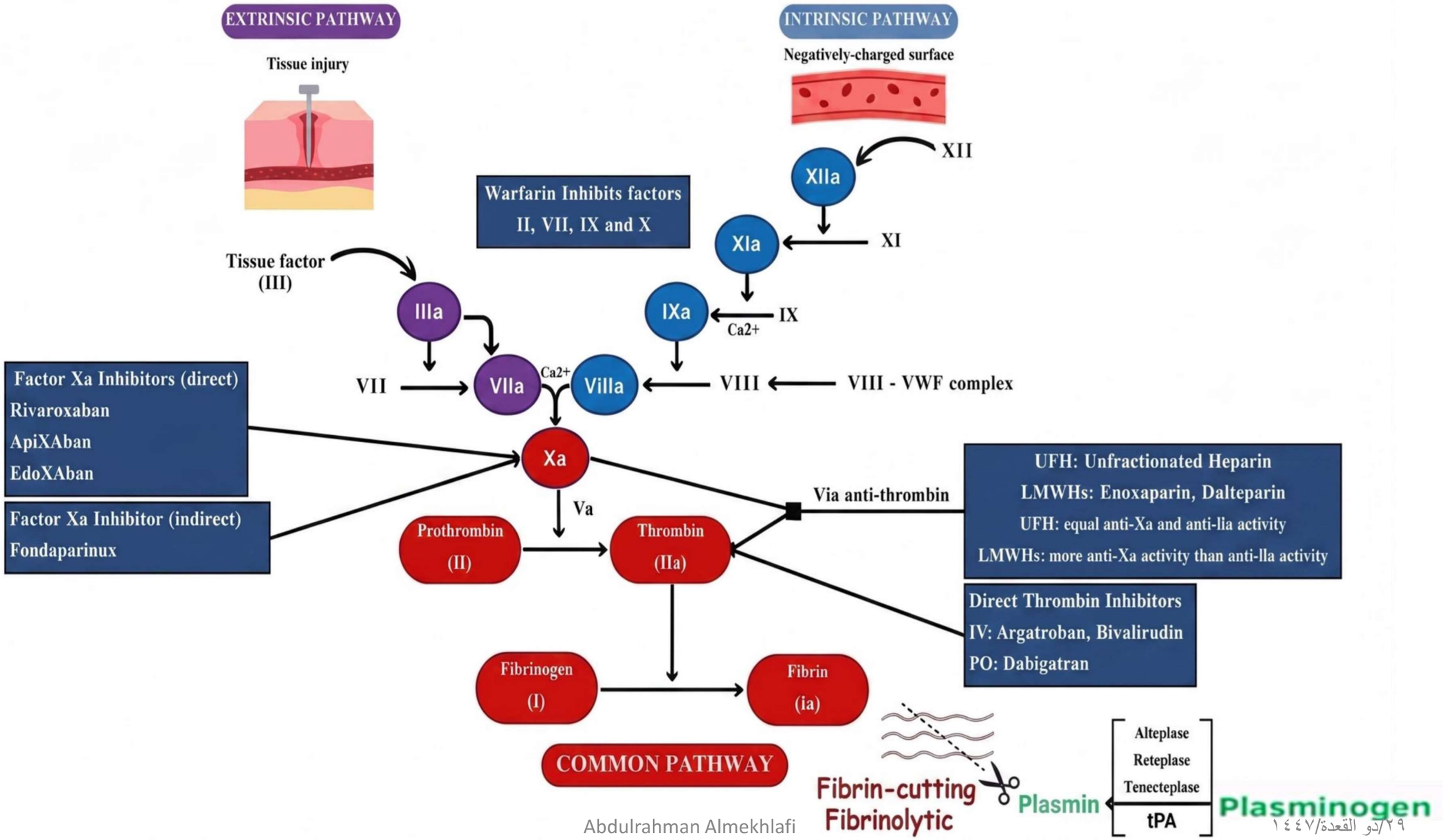
Prothrombin
(II)
Thrombin
(IIa)
Fibrinogen
(I)
Fibrin
(Ia)
COMMON PATHWAY
Plasmin
tPA
Plasminogen
2) PLATELET PLUG FORMATION
1. Plt activation
2. Plt adhesion
3. Plt release reaction
4. Plt aggregation


Anti-platelets
Gp1b
GpIIb/IIIa
GpIIb/IIIa inhibitors
(e.g, abciximab, eptifibatlde, tirofiban)
1) VASOCONSTRICTION
Von Willebrand factor
1
ADP
P2Y12
P2Y12 inhibitors
(e.g, clopidogrel, prasugrel,
ticagrelor, cangrelor)
Thromboxane A2
TxA2
Aspirin
via COX1/COX2 inhibation
2) PLATELET PLUG FORMATION
1. Plt activation
2. Plt adhesion
3. Plt release reaction
4. Plt aggregation

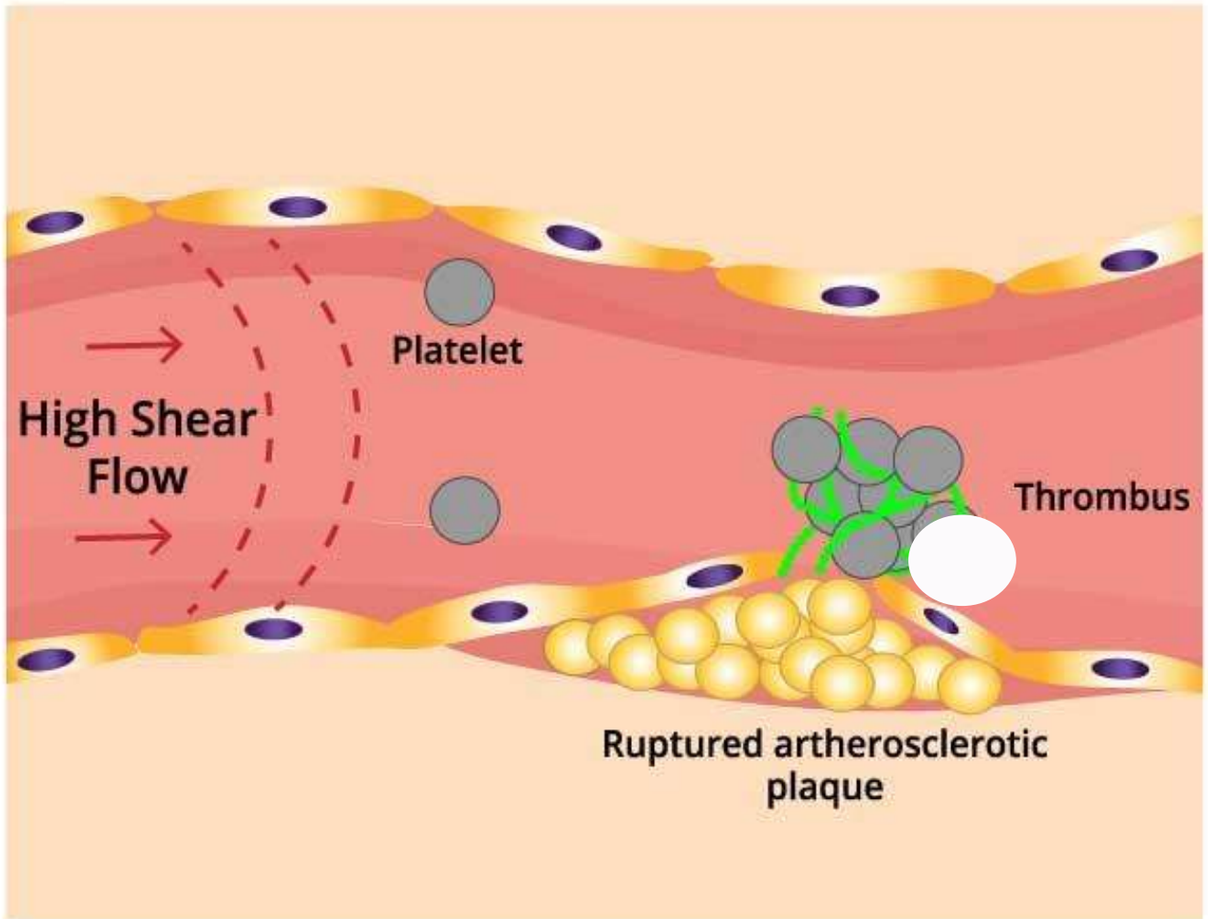
Coagulation Cascade



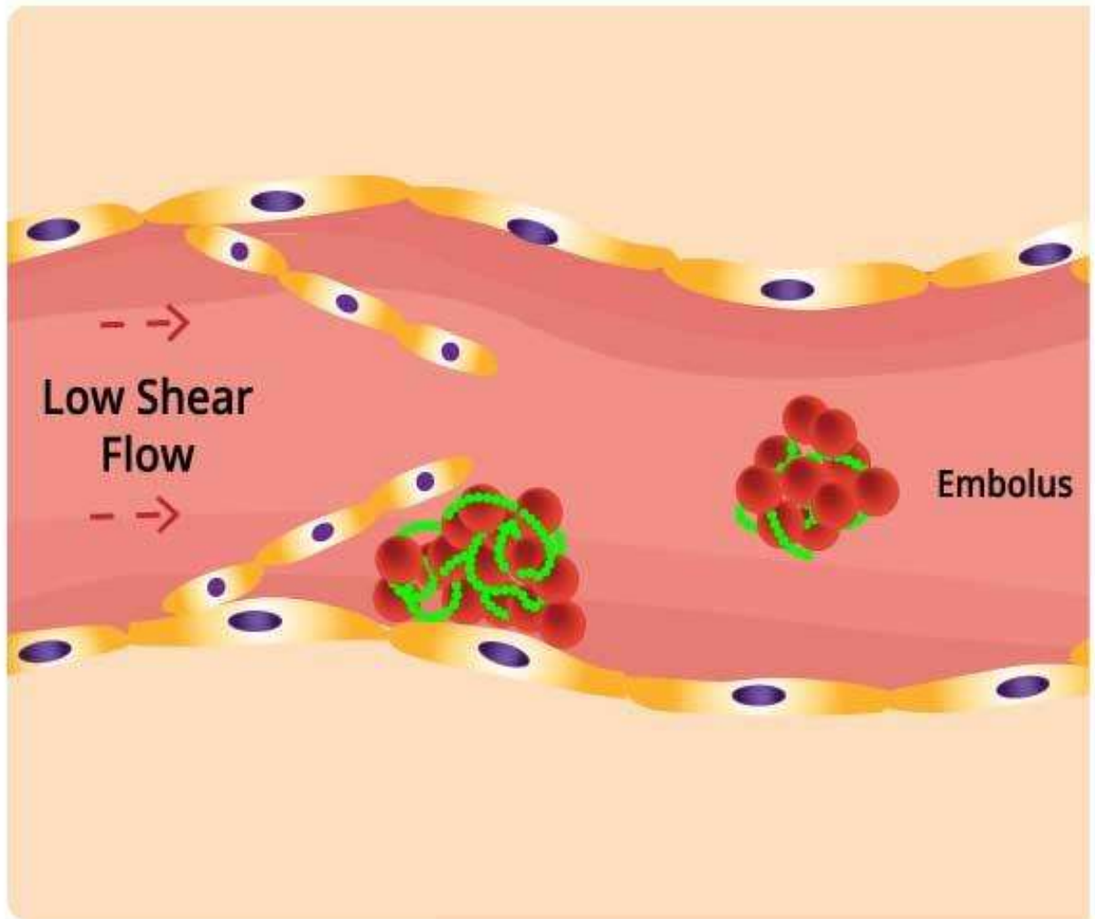
Anti-coagulation



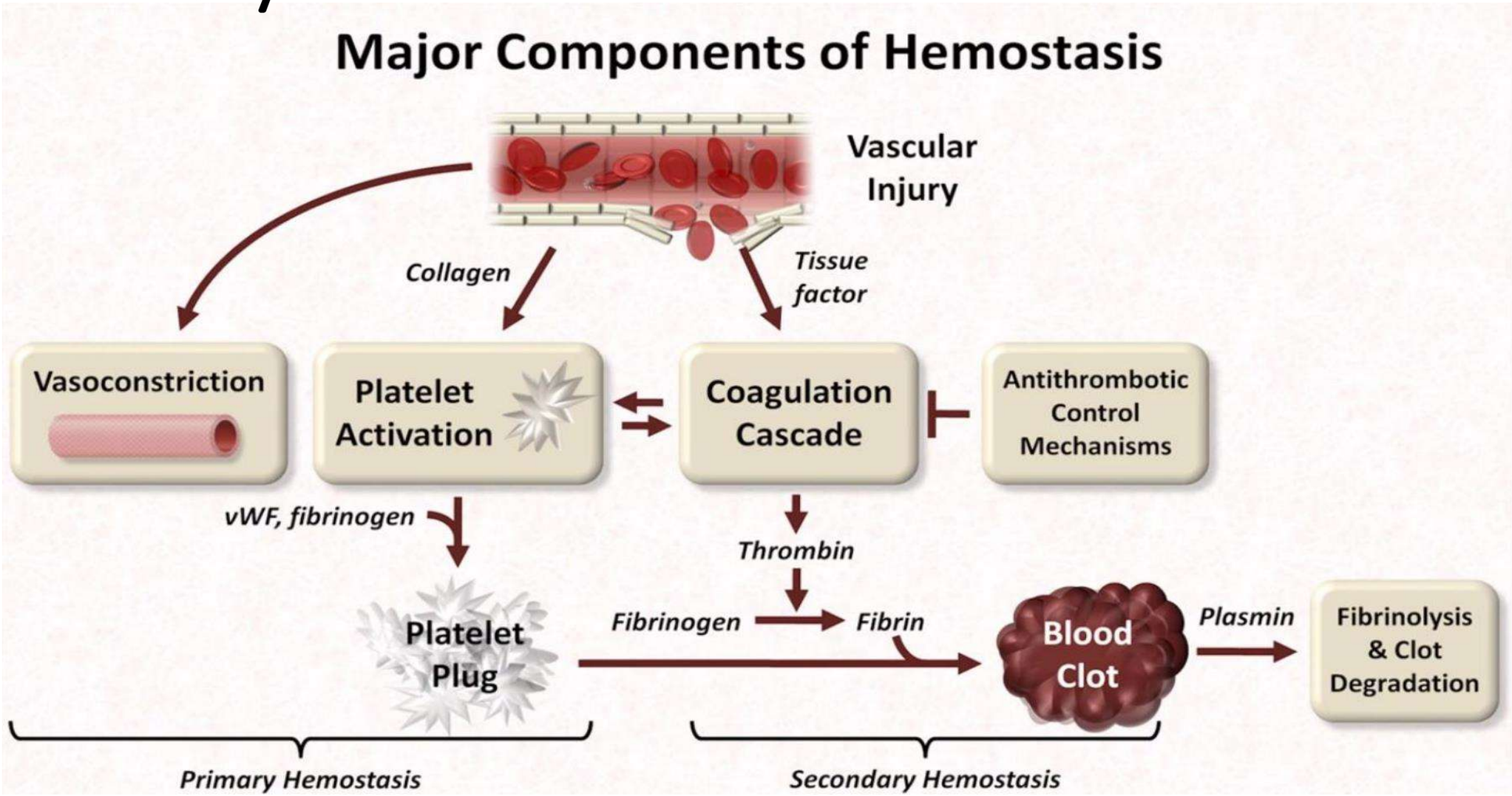
Arterial Thrombosis



Venous Thrombosis

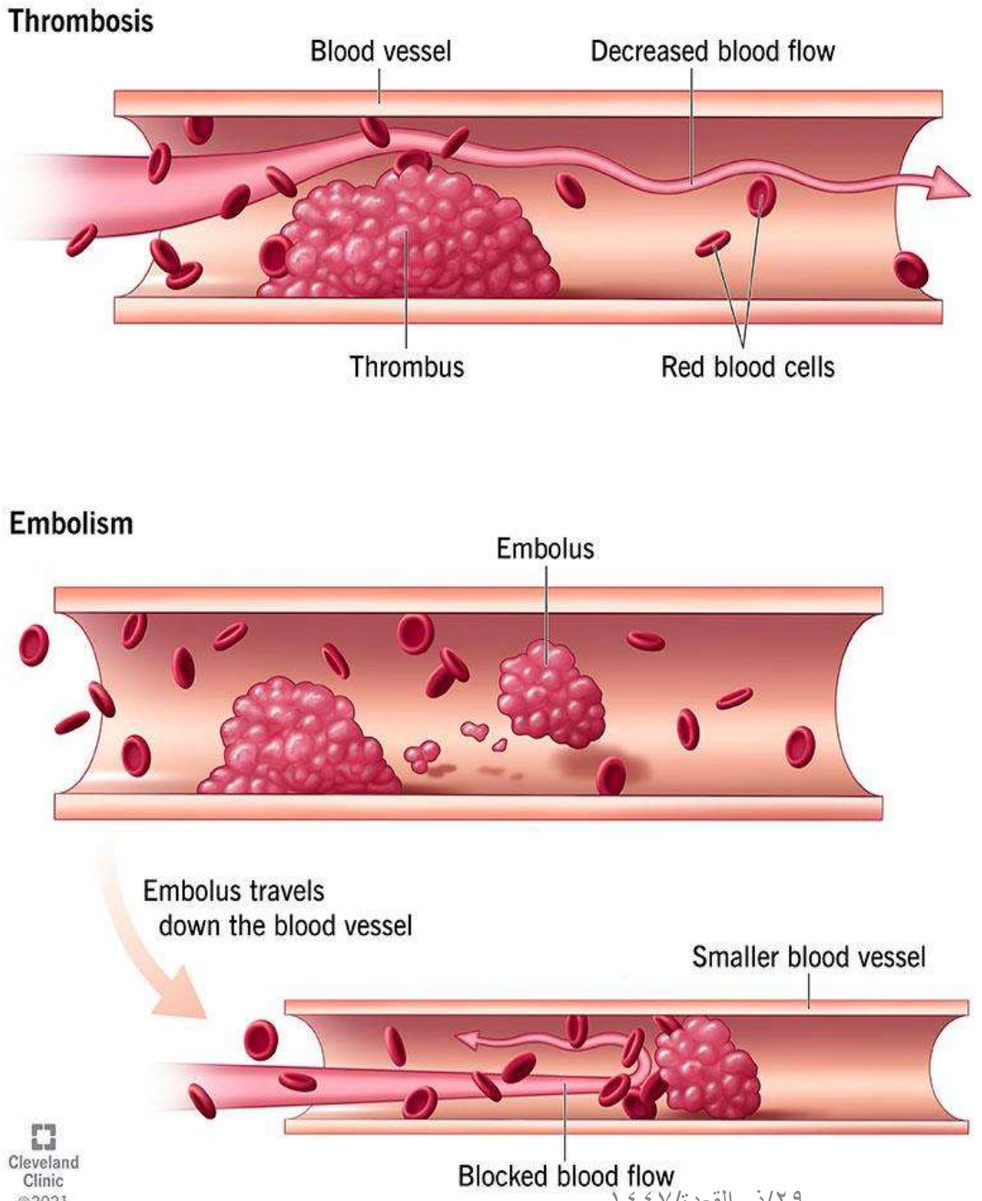


Summary


Major Components of Hemostasis
Vascular Injury
Collagen
Tissue factor
Vasoconstriction
Platelet Activation
Coagulation Cascade
Antithrombotic Control Mechanisms
vWF, fibrinogen
Thrombin
Platelet Plug
Fibrinogen
Fibrin
Blood Clot
Plasmin
Fibrinolysis & Clot Degradation
Primary Hemostasis
Secondary Hemostasis

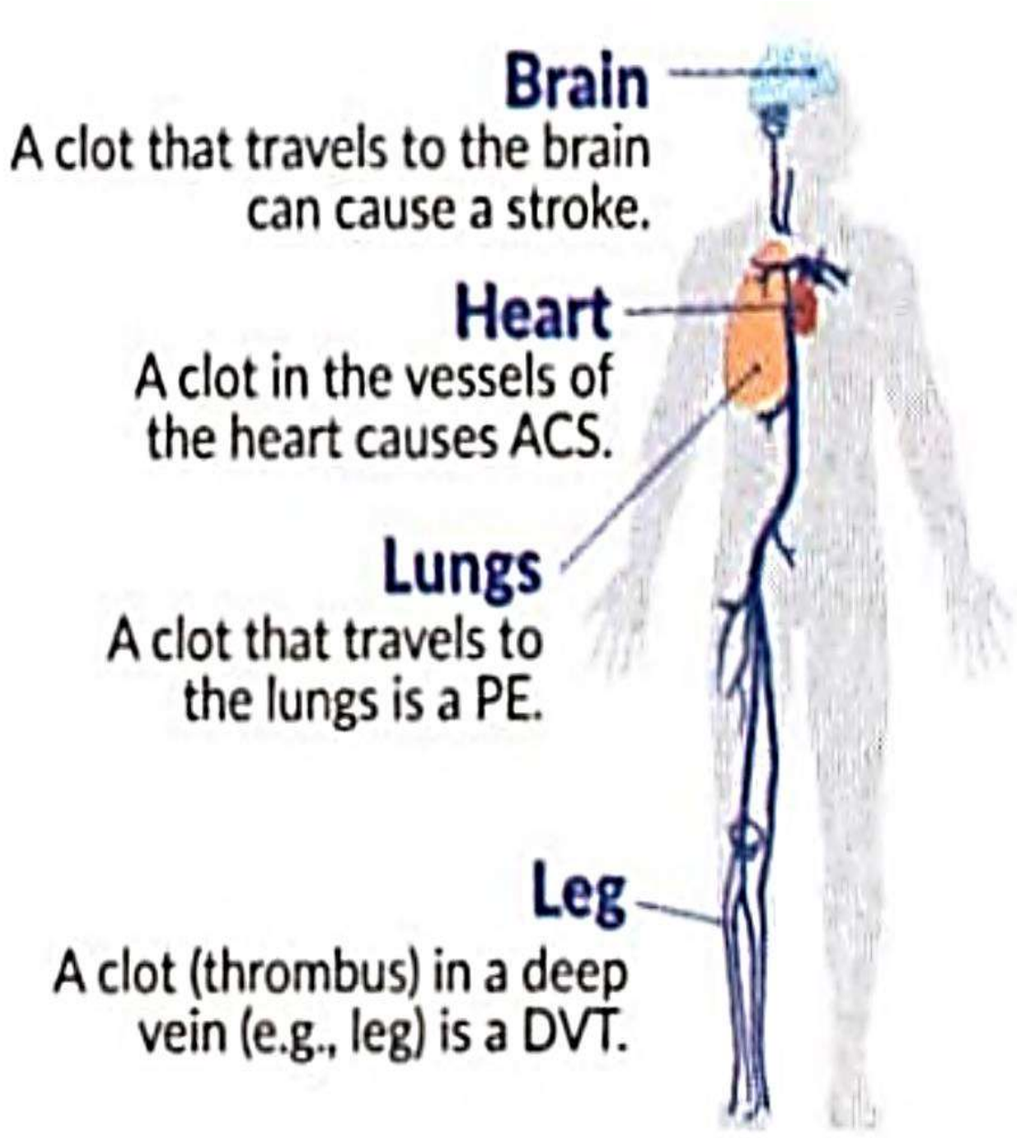
Thrombus vs embolus

- A **thrombus** is a blood clot that **forms and stays** attached to a blood vessel wall, obstructing flow at its origin (like DVT).
- While an **embolus** is **a piece of a thrombus** (or other material) that breaks off, travels through the bloodstream, and gets stuck somewhere else, blocking blood flow at a new site (like a pulmonary embolism).

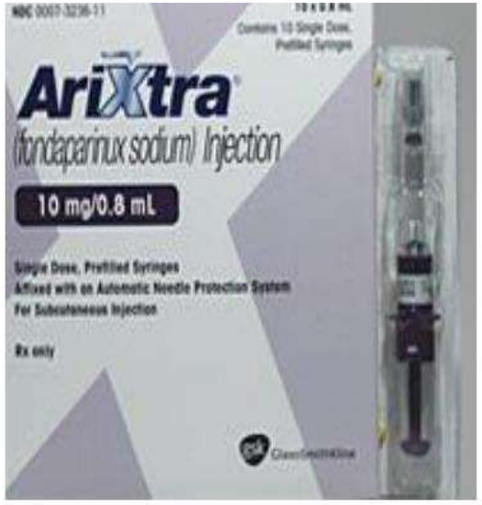


Anticoagulants

- **Anticoagulants** are used to **prevent blood clots from forming** and to keep existing clots from **becoming larger.** They do not break down clots (like fibrinolytics). Anticoagulants are used in the **prevention** and **treatment** of venous thromboembolism **(VTE),** which refers to deep vein thrombosis **(DVT)** and/or pulmonary embolism **(PE).**
- Anticoagulants are also used in the immediate treatment of acute coronary syndromes **(ACS)** and for the prevention of cardioembolic **stroke.** The most common *side effect* of anticoagulants is **bleeding**, which can be fatal. Anticoagulants are high-alert medications for this reason.


Brain
A clot that travels to the brain can cause a stroke.
Heart
A clot in the vessels of the heart causes ACS.
Lungs
A clot that travels to the lungs is a PE.
Leg
A clot (thrombus) in a deep vein (e.g., leg) is a DVT.

Overview of Drugs



Antithrombotic Agents

Anti-coagulant

1. **Parenteral agents:**
   - i. **Heparin:**
     - Unfractionated Heparin (UFH)
     - Low Molecular Weight Heparins (LMWH)
   - ii. **Fondaparinux**
   - iii. **Direct thrombin inhibitors:**
     Argatroban and Bivalirudin
2. **Oral agents:**
   - i. **Vit K epoxide reductase inhibitor**
     Warfarin
   - ii. **Direct Xa inhibitors:**
     Rivaroxaban, Apixaban and Edoxaban
   - iii. **Direct thrombin inhibitors:**
     Dabigatran

Antiplatelets

1. **Thromboxane A2 inhibitors**
   Aspirin
   Dipyridamole
2. **Glycoprotein IIb/IIIa inhibitors (IV)**
   Abciximab
   Eptifibatide
   Tirofiban
3. **P2Y12 receptor antagonists**
   Clopidogrel
   Ticagrelor
   Prasugrel
   Cangrelor (IV)

Fibrinolytics (t-PA): Alteplase, Streptokinase, Tenecteplase and Reteplase

Protocol Administration of Heparin (UFH)

- **IV infusion:**

  25,000 units in 250 mL (concentration: 100 units/mL) of ***D5W***, or ***NS***

- **Administration IV:**

  IV Continuous IV infusion: Infuse via infusion pump.

  If preparing solution, mix thoroughly prior to administration.

  Catheter patency: Practice is variable. If used for this purpose, refer to institution-specific protocols. The intention is only to maintain patency of IV catheters and is not to be used for anticoagulant therapy.

- Do **not** administer **IM** due to pain, irritation, and hematoma formation.

- **Administration SC:**

  Subcutaneous Inject in subcutaneous tissue only **(not muscle tissue).** Injection sites should be rotated (usually left and right portions of the abdomen, above iliac crest)

Protocol Administration of Heparin

Table 1. Initiation of IV Heparin Infusion (For all patient care units)

LOW Dose Protocol: acute coronary syndrome, atrial fibrillation, concomitant thrombolytic therapy, peripheral artery disease, or therapeutic anticoagulation desired but patient is at a high risk of bleeding due to acute condition, previous history of bleeding

Initial Bolus Dose (Optional)	Initial Infusion Dose
60 units/kg - Round to closest 100 units - Maximum bolus dose of 5,000 units - Bolus dose administered over 3 minutes	12 units/kg/hr - Round to closest 50 units/hr - Maximum initial dose 1,000 units/hr - Order defaults to duration of 24 hours

HIGH Dose Protocol: DVT, PE, mechanical valve replacement

Initial Bolus Dose (Optional)	Initial Infusion Dose
80 units/kg - Round to closest 100 units - Maximum bolus dose of 10,000 units - Bolus dose administered over 3 minutes	18 units/kg/hr - Round to closest 50 units/hr. - Maximum initial rate of 2,000 units/hr - Order defaults to a duration of 24 hours

Table 2. Maintenance Dose Adjustments Based on aPTT Results for Non-intensive Care Units

aPTT (sec)	Bolus	Maintenance Infusion Dosage Change	Next aPTT After Change
<45	40 units/kg* ***Refer table 3 below for bolus dose adjustment***	Increase rate by 3 units/kg/hr	6 hours
45-59	NONE	Increase rate by 2 units/kg/hr	6 hours
60-80 (Goal)	NONE	NO CHANGE	6 hours until therapeutic x 2 consecutive values, then q24h
81-90	NONE	Decrease rate by 3 units/kg/hr	6 hours
> 90	NONE	**STOP** infusion for 2 hours, Then, decrease rate by 3 units/kg/hr	2 hours after infusion resumed

Table 3. Bolus Dose Adjustment (40 units/kg) for Non-intensive Care Units

Patient Weight (kg)	<60 kg	60-85 kg	85-110 kg	>110 kg
Dose	2,000 units	3,000 units	4,000 units	5,000 units Maximum

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Table 4. Maintenance Dose Adjustment Heparin IV Nomogram for Intensive Care Units (Target aPTT 60-80 seconds)

MAINTENANCE IV HEPARIN ORDERS: Adjust IV Dose Based on Subsequent aPTT As Per Table.							
aPTT (sec)	BOLUS (Round to nearest 100 units)	Dosage Change	Dosage Change Based on Weight* (Round Doses to Nearest 50 units/hr.)				NEXT aPTT After Change
			40-59 kg	60-69 kg	70-79 kg	>80 kg	
< 35	60 units/kg = ____ units	+ 3 units/kg/hr	↑ by 150 units/hr	↑ by 200 units/hr	↑ by 250 units/hr	↑ by 300 units/hr	6 hours
35-44	30 units/kg = ____ units	+ 2 units/kg/hr	↑ by 100 units/hr	↑ by 150 units/hr	↑ by 150 units/hr	↑ by 200 units/hr	6 hours
45-59	NONE	+ 2 units/kg/hr	↑ by 100 units/hr	↑ by 150 units/hr	↑ by 150 units/hr	↑ by 200 units/hr	6 hours
60-80 (Goal)	NONE	NO CHANGE	NO CHANGE				24 hours
81-95	NONE	- 2 units/kg/hr	↓ by 100 units/hr	↓by 150 units/hr	↓ by 150 units/hr	↓ by 200 units/hr	6 hours
> 95	NONE	**STOP x 1 hour; Restart at – 3 units/kg/hr**	↓ by 150 units/hr	↓ by 200 units/hr	↓ by 250 units/hr	↓ by 300 units/hr	6 hours

Protocol Administration of Warfarin

- ✓ Before initiating warfarin therapy, the patient should be **assessed for risk factors** that may increase their risk for bleeding, thromboembolic events and for risk factors that may impact the sensitivity of the response to warfarin.
- ✓ **Patients with multiple high sensitivity risk factors** may require a **lower initiation** dose (2.5 mg) and reduced maintenance doses.

Examples of these risk factors

Increased Warfarin Sensitivity	
Increased INR Response:	Increased Bleeding Risk:
1. Baseline INR ≥ 1.5	1. Current antiplatelet therapy
2. Age > 65	2. Thrombocytopenia: platelet <75 K/uL
3. Actual body weight < 45 kg or actual < ideal	3. Significant hepatic disease: cirrhosis or total bilirubin.>2.4 mg/dL
4. Malnourished/ NPO >3 days	4. Alcohol abuse history
5. Hypoalbuminemia <2 g/dl	5. End stage renal disease
6. Chronic diarrhea	6. GI bleed within past 30 days
7. Significant drug interactions	7. Surgery within past 2 weeks
8. Decompensated heart failure	8. Intracranial bleed within past 30 days

MAREVAN brand warfarin tablets:

- 1 mg tablet (brown)
- 3 mg tablet (blue)
- 5 mg tablet (pink).

Protocol Administration of Warfarin

- Oral Administer **with or without food.**
- In clinical practice, patients are often encouraged to **take their dose later** in the day to facilitate implementation of needed dose changes identified.
- **Onset of action:** Initial anticoagulant effect on INR may be seen as soon as 24 to 72 hours.

  Note: Full therapeutic effect generally seen between 5 and 7 days after initiation; dependent on reduction in vitamin K-dependent coagulation factors, especially prothrombin (factor II), which has a half-life of 60 to 72 hours
- **Food Interactions:**
  i. The anticoagulant effects of warfarin may be **decreased** if taken with **foods rich in vitamin K**.
  ii. Cranberry juice & Vitamin E may **increase** warfarin effect.
  iii. Management: Maintain a **consistent diet**; consult prescriber before making changes in diet.
  iv. Take warfarin at the same time each day

Protocol Administration of Warfarin

- Initial: **5 mg once daily** for most patients. A lower or higher starting dose may be used depending upon patient-specific factors.
- Although an elevation in INR can be seen as soon as 24 to 48 hours after the first dose due to depletion of factor VII, this does not represent therapeutic anticoagulation because other vitamin K–dependent clotting factors with longer half-lives (e.g. factors II, IX, and X) must also be depleted.
- Accordingly, in patients at **high risk for thromboembolism**, **overlap "bridging"** with a **parenteral anticoagulant** may be **necessary** during initiation (or monitoring) of warfarin until a stable therapeutic INR is attained.

Day	INR	DOSE (MG)
1	—	5.0
2	—	5.0
3	< 1.5	10.0
	1.5 to 1.9	5.0
	2.0 to 3.0	2.5
	> 3.0	0.0
4	< 1.5	10.0
	1.5 to 1.9	7.5
	2.0 to 3.0	5.0
	> 3.0	0.0
5	< 2.0	10.0
	2.5 to 3.0	5.0
	> 3.0	0.0
6	< 1.5	12.5
	1.5 to 1.9	10.0
	2.0 to 3.0	7.5
	> 3.0	0.0

Table 15 Maintenance warfarin dosing for out-of-therapeutic-range international normalized ratio

INR	Dose adjustment per week
≤1.5	↑ by 15%/week
1.6–1.9	↑ by 10%/week
2–2.9	Unchanged
3–3.9	↓ by 10%/week
4–4.9	Hold 1 dose, then restart with dose ↓ by 10%/week
≥5	Hold until INR is 2–3, then restart with dose ↓ by 15%/week

Suggested dose adjustment in case of out-of-therapeutic-range INR.[556] Importantly, dosing is optimized not using daily dose adjustments but adjustments based on the weekly intake in warfarin.

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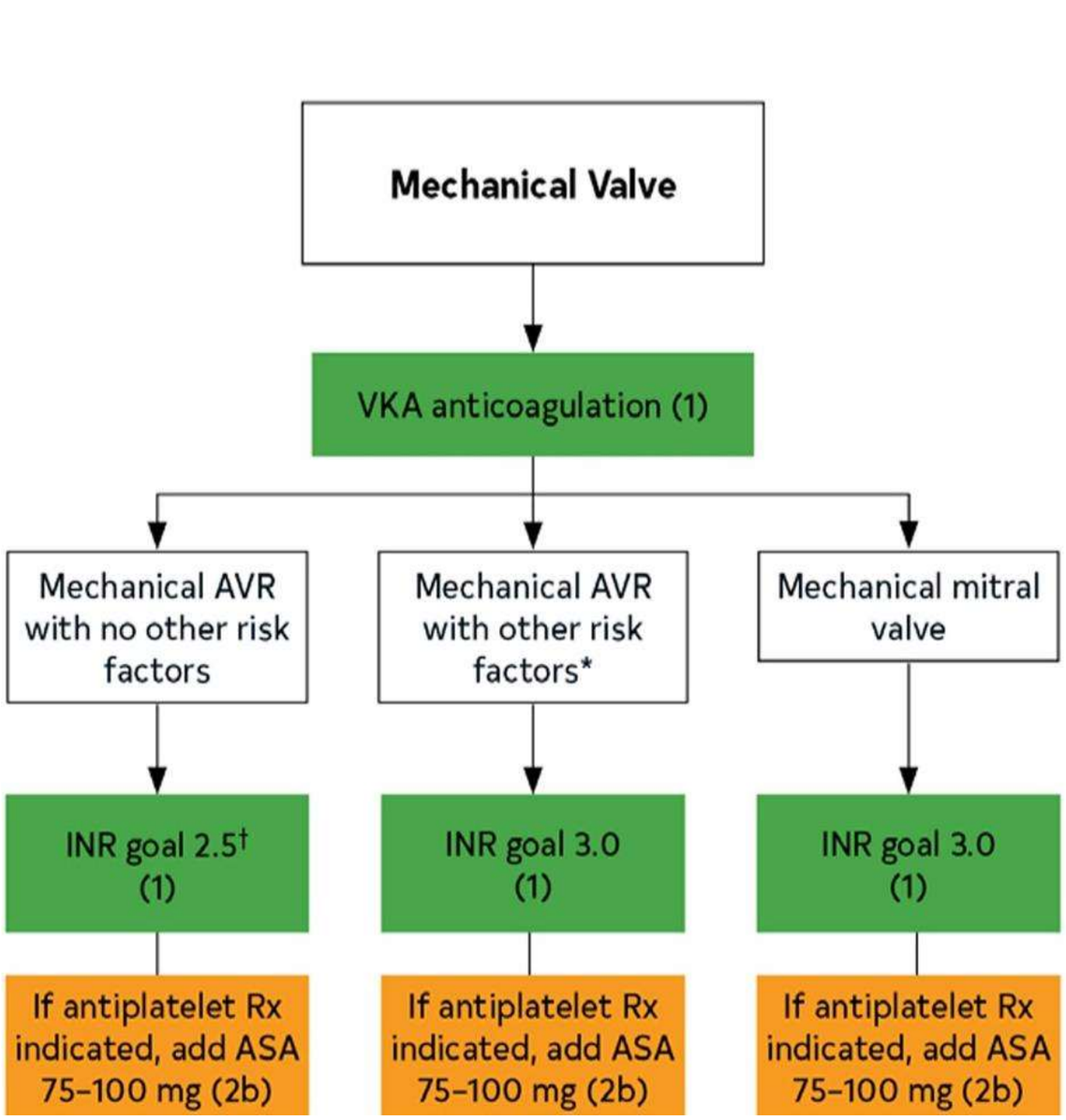
Protocol Administration of Warfarin

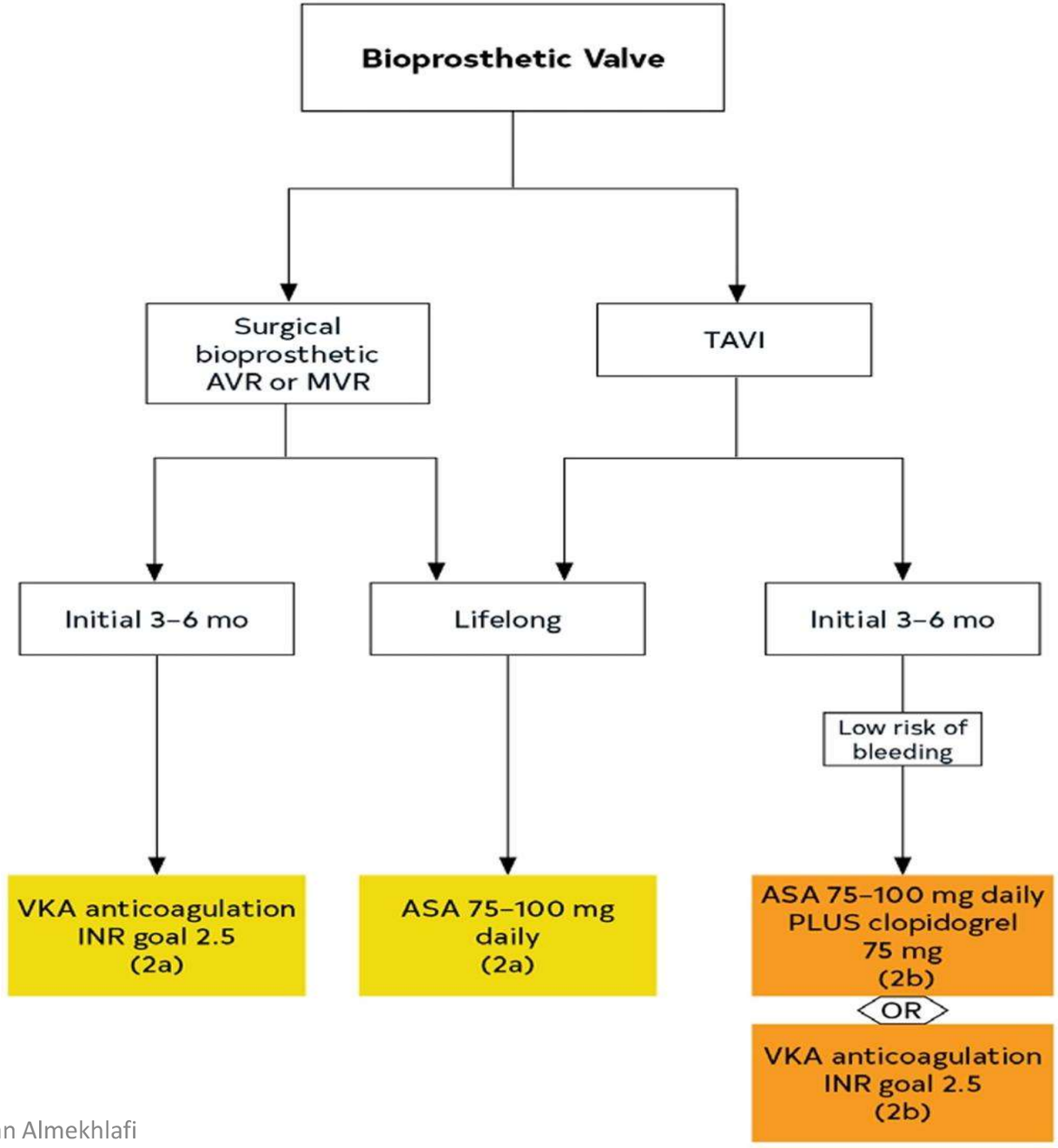
- **Dose Adjustment :**
  - Renal Impairment: No dosage adjustment necessary. However, patients with renal impairment have an increased risk for bleeding diathesis; monitor INR closely.
  - Hepatic Impairment: Adult There are no dosage adjustments provided in the manufacturer's labeling. However, the response to oral anticoagulants may be markedly enhanced in obstructive jaundice, hepatitis, and cirrhosis. INR should be closely monitored.
- **Monitoring:**
  a. **Before** making any dosing change the **clinical pharmacist should take** into account the recent **INR trends, changes in diet and/or activity, or changes to medications**
  b. Warfarin doses **must not be adjusted** without **a resulted INR**
  c. If the patient was previously stable on warfarin and presents with an isolated INR of 0.5 or less above or below therapeutic range, the current dosage should be continued and the patient retested in one to two weeks.

Indications of Antithrombotic

I. Valvular Heart Disease

Dr. Mohamed Amraan


Mechanical Valve
VKA anticoagulation (1)
Mechanical AVR with no other risk factors
Mechanical AVR with other risk factors*
Mechanical mitral valve
INR goal 2.5† (1)
INR goal 3.0 (1)
INR goal 3.0 (1)
If antiplatelet Rx indicated, add ASA 75–100 mg (2b)
If antiplatelet Rx indicated, add ASA 75–100 mg (2b)
If antiplatelet Rx indicated, add ASA 75–100 mg (2b)


Bioprosthetic Valve
Surgical bioprosthetic AVR or MVR
TAVI
Initial 3–6 mo
Lifelong
Initial 3–6 mo
Low risk of bleeding
VKA anticoagulation INR goal 2.5 (2a)
ASA 75–100 mg daily (2a)
ASA 75–100 mg daily PLUS clopidogrel 75 mg (2b)
OR
VKA anticoagulation INR goal 2.5 (2b)

II. Stroke Prevention in Nonvalvular Atrial Fibrillation

Dr. Mohamed Amraan

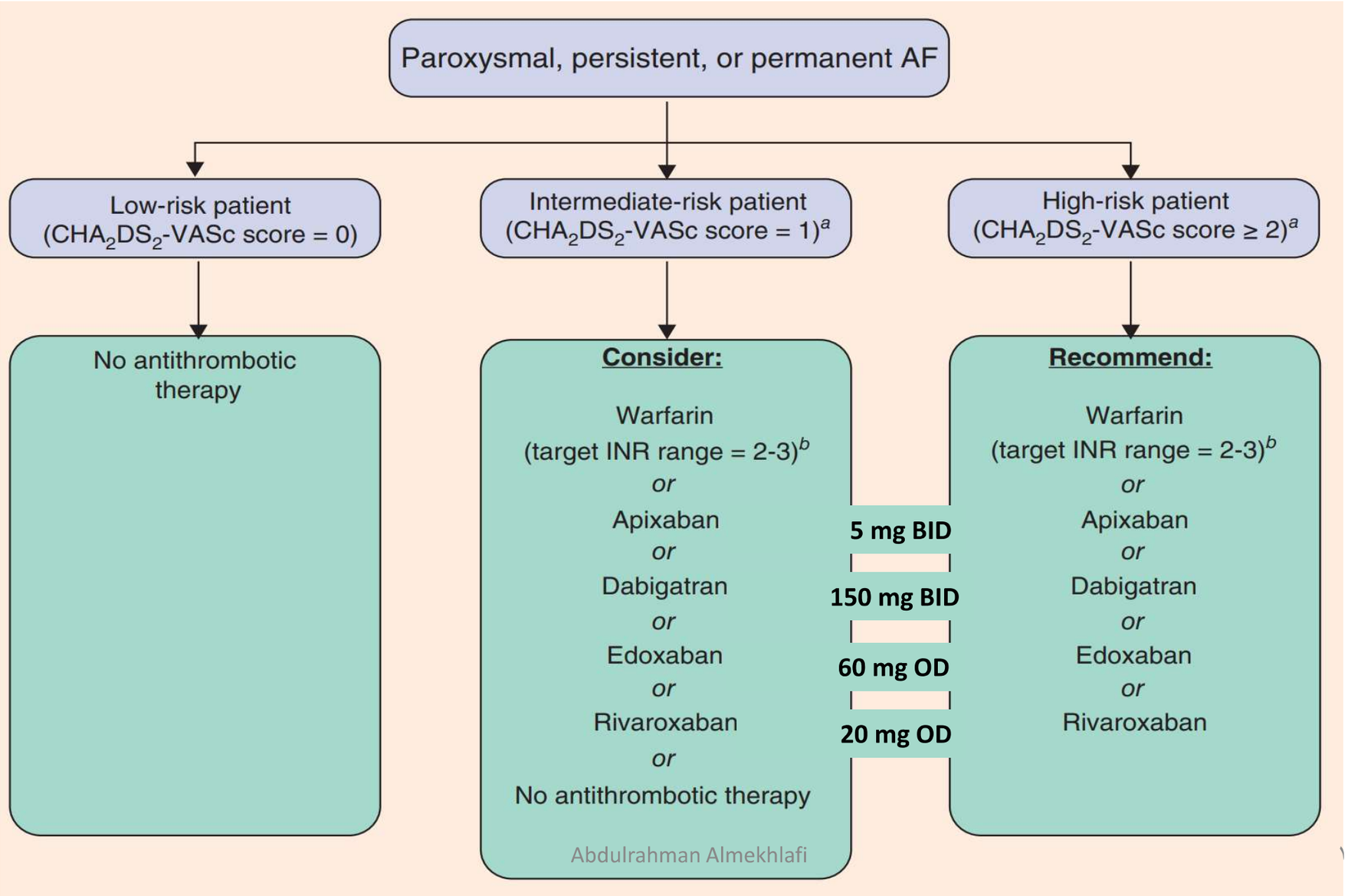
Risk Stratification for Ischemic Stroke in Patients with NVAF

$CHADS_2$ Score		CHA_2DS_2-VASc Score	
Congestive heart failure[a]	1	Heart failure[a]	1
Hypertension	1	Hypertension	1
Age ≥ 75	1	Age ≥ 75	2
Diabetes	1	Diabetes	1
Previous stroke or TIA or thromboembolism	2	Previous stroke or TIA or thromboembolism	2
		Vascular disease (CAD, PAD, aortic plaque)	1
		Age 65–74	1
		Sex category (female)	1

Guideline Recommendations for Antithrombotic Therapy in Patients with NVAF Based on CHA2 DS2 -VASc Score

CHA_2DS_2-VASc Score = 0 in men or 1 in women	CHA_2DS_2-VASc Score = 1 in men or 2 in women	CHA_2DS_2-VASc Score ≥ 2 in men or ≥ 3 in women
Omit antithrombotic therapy	Oral anticoagulation is reasonable (Level 2a recommendation)[b]	Oral anticoagulant therapy is indicated; DOACs are recommended over warfarin in DOAC-eligible patients (Level 1 recommendation)[b]

Prevention of thromboembolism in atrial fibrillation



Abdulrahman Almekhlafi

III. Prevention of Venous Thromboembolism

Dr. Mohamed Amraan

Thrombosis Risk Classification and Recommended Venous Thromboembolism Prevention Strategies

Indication and Level of Risk	Prevention Strategies
Hospitalized Medical Patients	
Low thrombosis risk	Early ambulation
High thrombosis risk[a] (Padua score > 4)	LMWH, LDUH, fondaparinux, betrixaban
Critically Ill Patients	
High thrombosis risk[a]	LMWH, LDUH
General Surgical Patients	
Very low thrombosis risk (Caprini Score 0)	Early ambulation
Low thrombosis risk (Caprini Score 1–2)	IPC
Moderate thrombosis risk[b] (Caprini Score 3–4)	LMWH, LDUH, IPC
High thrombosis risk[b] (Caprini Score ≥ 5)	LMWH, LDUH, plus GCS or IPC
Cancer Surgery	LMWH, rivaroxaban, apixaban
Major Orthopedic Surgery	
Hip fracture surgery[b]	LMWH, fondaparinux, LDUH, adjusted dose warfarin, aspirin
Hip and knee arthroplasty[b]	LMWH, fondaparinux, LDUH, warfarin, aspirin, apixaban, dabigatran, rivaroxaban

[a]Mechanical methods of prophylaxis with IPC or GCS should be used in patients actively bleeding or those at high risk of bleeding complications (see **Table 11–6** for risk factors for major bleeding).

[b]Mechanical methods of prophylaxis with IPC should be used in patients actively bleeding or those at high risk of bleeding complications (see **Table 11–6** for risk factors for major bleeding).

GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin.

IV. Treatment of Venous Thromboembolism

Dr. Mohamed Amraan

Acute Treatment of VTE

1. **Three approaches** to VTE treatment (Table 22).
2. The 2021 American College of Chest Physicians guidelines prefer DOACs to warfarin for patients with VTE **without cancer** because of reduced bleeding risk and greater convenience for patients and health care providers.
3. The 2020 ASH guidelines also **prefer DOACs** to warfarin for the treatment of VTE.

Table 22. Approaches to VTE Treatment

Treatment Strategy	Anticoagulant Choices
Bridging therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) initiated with warfarin and overlapped for at least 5 days and until the INR is ≥ 2.0. Then discontinue injectable anticoagulant and continue warfarin dose-adjusted to INR target of 2.5 (±0.5) for indicated duration
Switching therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) for first 5 days; then discontinue injectable anticoagulant therapy and initiate dabigatran or edoxaban for the indicated duration
Monotherapy	Initiate rivaroxaban or apixaban at higher initial dose and then convert patient to lower maintenance dose for the indicated duration

Acute Treatment of VTE

Table 23. Dosing of Injectable Anticoagulants for VTE Treatment

Agent and Route	Dosing
Unfractionated Heparin (IV)	
IV UFH[a]	Weight adjusted with an initial bolus of 80 units/kg (max initial bolus of 10,000 units), followed by an initial infusion of 18 units/kg/hr (max initial infusion of 2000 units/hr). Subsequent doses should be adjusted to maintain the institution's goal aPTT
Low-Molecular-Weight Heparin (SC)	
Enoxaparin	1 mg/kg q12hr or 1.5 mg/kg q24hr[b]; if CrCl < 30 mL/min, administer 1 mg/kg q24hr
Dalteparin[c,d]	100 units/kg q12hr or 200 units/kg q24hr; CrCl < 30 mL/min – Contraindicated
Pentasaccharide (SC)	
Fondaparinux	Weight < 50 kg – Administer 5 mg q24hr Weight 50–100 kg – Administer 7.5 mg q24hr Weight > 100 kg – Administer 10 mg q24hr CrCl < 30 mL/min – Contraindicated

Acute Treatment of VTE

➢ Thrombolysis for the Treatment of Venous Thromboembolism

- Thrombolytic therapy should be reserved for patients who present with:
  i. PE with **shock**,
  ii. **hypotension**, or
  iii. **massive** DVT with limb **gangrene**
- Diagnosis must be objectively confirmed before initiating thrombolytic therapy
- Thrombolytic therapy is most effective when administered ***as soon as possible*** after PE diagnosis, but benefit may extend **up to 14 days** after symptom onset
- FDA-Approved PE Thrombolytic Regimens:
  i. Streptokinase 250,000 units IV bolus over 30 minutes followed by 100,000 units/hour for 12–24 hours
  ii. Urokinase 4400 units/kg IV bolus over 10 minutes followed by 4400 units/kg/hour for 12–24 hours
  iii. Alteplase (rt-PA) 100 mg IV over 2 hours

Table 11–13

Dosing of the Direct Oral Anticoagulants in the Treatment of Venous Thromboembolism (VTE) and Their Reversal Agents

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Acute VTE	150 mg BID after 5–10 days of parenteral anticoagulation	15 mg BID × 3 weeks then 20 mg once daily with food	10 mg BID for 7 days, then 5 mg BID	60 mg once daily
Prevention of VTE recurrence	150 mg BID	10 mg once daily with food (after 6 months of acute treatment)	2.5 mg BID (after 6 months of acute treatment)	n/a
Dosage adjustments and/or thresholds for avoidance	Any P-gp *inducer*: avoid concurrent use Any P-gp *inhibitor* with CrCl < 50 mL/min (0.83 mL/s): avoid concurrent use CrCl < 30 mL/min (0.50 mL/s): avoid use	CrCl 30–50 mL/min (0.50–0.83 mL/s): use with caution CrCl < 30 mL/min (0.50 mL/s): avoid use	Dual strong CYP3A4 and P-gp inhibitors: If dose > 2.5 mg BID, decrease by 50% If already taking 2.5 mg BID and dual strong CYP3A4 and P-gp inhibitor: avoid use No dose adjustment in renal impairment or end-stage renal disease required	CrCl 15–50 mL/min (0.25–0.83 mL/s) or body weight ≤ 60 kg (132 lb), or concurrent use with certain P-gp inhibitors: 30 mg once daily
FDA-approved reversal agent	Idarucizumab 5 g IV by infusion or bolus	Recombinant inactivated coagulation Factor Xa High dose: 800 mg IV bolus + 960 mg IV infusion Low dose: 400 mg IV bolus + 480 mg IV infusion	Recombinant inactivated coagulation Factor Xa High dose: 800 mg IV bolus + 960 mg IV infusion Low dose: 400 mg IV bolus + 480 mg IV infusion	n/a

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V. Antithrombotic Therapy for Ischemic Stroke

Thrombolysis

Table 10. Typical Inclusion/Exclusion Criteria for IV Alteplase and Tenecteplase for Ischemic Stroke[a]

Patient Selection Criteria	Patient History Excludes All Contraindications
Onset of symptoms < 4.5 hr from drug administration	Intracranial or intraspinal surgery within 3 mo
Baseline head CT excludes intracerebral hemorrhage (ICH) or other risk factors	Head trauma or stroke < 3 mo
Age ≥ 18 yr	Active internal or intracerebral bleeding
	Symptoms suggestive of SAH
Vital signs and laboratory values:	Any history of ICH
INR ≤ 1.7	Intracranial neoplasm, arteriovenous malformation, or aneurysm
Plt ≥ 100,000/mm^3	Arterial puncture at noncompressible site within 1 wk
Blood glucose > 50 mg/dL	Current SBP > 185 mm Hg or DBP > 110 mm Hg
Blood pressure control (SBP < 185 mm Hg, DBP < 110 mm Hg)	Current use of anticoagulant agents with evidence of elevated sensitive laboratory tests, including direct-acting oral anticoagulants and therapeutic doses of low-molecular-weight heparin

Table 12–5

Recommendations for Pharmacotherapy of Ischemic Stroke

	Primary Agents	Alternatives
Acute treatment	Alteplase 0.9 mg/kg IV (maximum dose 90 mg); 10% as IV bolus, remainder infused over 1 hour in select patients within 4.5 hours of onset Tenecteplase 0.25 mg/kg IV bolus (maximum dose 25 mg); may choose over alteplase prior to thrombectomy ASA 160–325 mg started within 48 hours of onset; hold for 24 hours if alteplase or tenecteplase given (may reduce dose to 50–100 mg daily after 48 hours)	Alteplase (various doses) intra-arterially within 6 hours after onset in select patients If minor stroke or TIA, ASA 75 mg plus clopidogrel 75 mg daily started within 24 hours of onset × 21 days
Secondary prevention (noncardioembolic stroke)	ASA 50–325 mg daily ASA 25 mg + ER dipyridamole 200 mg twice daily	Clopidogrel 75 mg daily
Cardioembolic	Warfarin (INR 2–3) Apixaban 5 mg twice daily; decrease to 2.5 mg twice daily if patient has at least two of the following: age ≥ 80 years, weight ≤ 60 kg (132 lb) or serum creatinine ≥ 1.5 mg/dL (133 µmol/L) Rivaroxaban 20 mg daily with the evening meal; decrease to 15 mg daily with the evening meal if CrCl 15–50 mL/min (0.25–0.83 mL/s)	Edoxaban 60 mg once daily; decrease to 30 mg once daily if CrCl 15–30 mL/min (0.25–0.50 mL/s) Dabigatran 150 mg twice daily; decrease to 75 mg twice daily if CrCl 15–30 mL/min (0.25–0.50 mL/s)
All patients	BP control Statin therapy	

Administration of Alteplase in Acute Ischemic Stroke

- The recommended dose is 0.9 mg/kg body weight (maximum 90 mg) **given in 2 parts**:
  i. **10%** of the total dose administered as an initial IV bolus
  ii. followed by the remaining **90%** of reconstituted alteplase administered as an IV infusion over 60 minutes
- Alteplase should **NOT** be mixed with other drugs, neither in the same infusion vial nor the same venous line (NOT even with heparin).

VI. Acute Coronary Syndrome

Antiplatelet Therapy

Table 4. Antiplatelet Management Strategies According to ACS Presentation

Antiplatelet	NSTE-ACS Conservative	NSTE-ACS Invasive	STEMI PCI	STEMI + Fibrinolytic
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
$P2Y_{12}$ receptor antagonist	Clopidogrel Ticagrelor	Clopidogrel Prasugrel[a] Ticagrelor[a] Cangrelor[b]	Clopidogrel Prasugrel[a] Ticagrelor[a] Cangrelor[b]	Clopidogrel[c] Ticagrelor[d]
GP IIb/IIIa inhibitor	Reserved for patients undergoing PCI with large thrombus burden, no-reflow, or slow flow			

[a]In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis (Class 2a, 2021 Guideline for Coronary Artery Revascularization).

[b]Cangrelor may be considered in patients undergoing PCI who are $P2Y_{12}$ inhibitor naïve (Class 2b, 2021 Guideline for Coronary Artery Revascularization).

[c]Pre-PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if more than 24 hr after event.

[d]Ticagrelor may be used as an alternative to clopidogrel in patients less than 75 years of age who undergo PCI within 24 hr of fibrinolytic administration (Class 2b, 2021 Guideline for Coronary Artery Revascularization).

Table 5. Guideline Recommendations for $P2Y_{12}$ Inhibitor Therapy in ACS with or without PCI[a]

Guideline Recommendation	Class/Grade
An LD of $P2Y_{12}$ receptor inhibitor should be given in patients with ACS who undergo PCI. Options include: a. Clopidogrel[b] 600 mg, followed by 75 mg daily b. Prasugrel 60 mg, followed by 10 mg daily[c]; or c. Ticagrelor 180 mg, followed by 90 mg BID • 2021 ACC/AHA guideline for coronary artery revascularization	1 LOE B LOE B LOE B
For patients with NSTE-ACS treated with PCI or patients with NSTE-ACS treated with medical therapy alone: a. Clopidogrel 600 mg, followed by 75 mg daily b. Ticagrelor 180 mg, followed by 90 mg BID • 2014 NSTE-ACS guideline	1 LOE B LOE B
For patients with ACS treated with an early invasive or conservative strategy: It is reasonable to use **ticagrelor** in preference to clopidogrel • 2021 ACC/AHA guideline for coronary artery revascularization • 2016 ACC/AHA focused update on duration of DAPT	2a LOE B
For patients with ACS treated with PCI: It is reasonable to choose **prasugrel** over clopidogrel • 2021 ACC/AHA guideline for coronary artery revascularization	2a LOE B
Prasugrel should not be administered to patients with a history of TIA or stroke • ٤٢2021 ACC/AHA guideline for coronary artery revascularization	Class 3

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Antiplatelet Therapy

Table 7. GP IIb/IIIa Inhibitor Dosing

	Dosing for Patients Undergoing PCI	**Renal Adjustments**
Eptifibatide (Integrilin)	180 mcg/kg IV bolus × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for up to 18 hr	If CrCl < 50 mL/min/1.73 m^2, reduce infusion 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL
Tirofiban (Aggrastat)	25 mcg/kg IV bolus over 3 min; then 0.15 mcg/kg/min for up to 18 hr	If CrCl ≤ 60 mL/min/1.73 m^2, reduce infusion 50%

CrCl = creatinine clearance; IV, intravenous; SCr = serum creatinine.

Anticoagulant Therapy

Table 8. Anticoagulant Management Strategies in ACS[a]

	Class 1 Recommendations
STEMI (PPCI)	UFH, bivalirudin[c]
STEMI, with fibrinolytic[b] therapy	UFH, enoxaparin, fondaparinux
NSTE-ACS, early invasive strategy	Bivalirudin[c] UFH
NSTE-ACS, conservative (medical) strategy	Enoxaparin, fondaparinux[d] UFH

[a]Class 1, should be performed or administered; class 2a, reasonable to be performed or administered; class 2b, may be considered; class 3, not to be administered or harmful.

[b]Fibrinolytics preferred when PCI cannot be performed within 120 min of first medical contact (class 1). Door-to-needle time < 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hr with intravenous UFH or IV/SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

[c]Bivalirudin should be used in patients with heparin-induced thrombocytopenia (class 1); reasonable alternative to UFH to reduce bleeding (class 2b).

[d]Fondaparinux should not be used as the sole anticoagulant to support PCI. Give additional anticoagulant during revascularization if fondaparinux was initially chosen as the anticoagulant strategy. Fondaparinux is given a class 1 recommendation in the 2014 NSTE-ACS guidelines (for a conservative strategy) and a class 3 or harmful recommendation in the 2022 coronary artery revascularization guidelines when PCI is indicated.

Table 9. Antithrombotic Dosing in ACS with or without PCI

	UFH	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
Classification	Indirect thrombin inhibitor	LMWH	Factor Xa inhibitor	Direct thrombin inhibitor
NSTE-ACS	60–70 units/kg IVB (max 4000 units), 12 units/kg/hr IV (max 1000 units/hr) for 48 hr or until PCI performed; goal aPTT/anti-Xa according to hospital-specific protocol	1 mg/kg SC every 12 hr for 24–48 hr or until PCI performed or throughout hospitalization (up to 8 days); 30 mg IVB	2.5 mg SC daily	0.1 mg/kg IVB; then 0.25 mg/kg/hr IV (only for planned invasive strategy)
PCI	Supplemental doses to target ACT[a] If GP IIb/IIIa inhibitors, UFH 50–70 units/kg IVB If no GP IIb/IIIa inhibitors, UFH 70–100 units/kg IVB	If last dose < 8 hr, nothing additional needed If last dose was 8–12 hrs earlier or only 1 SQ dose was administered before PCI, 0.3 mg/kg IVB	Fondaparinux should not be used as a sole anticoagulant for PCI	0.75 mg/kg IVB, 1.75 mg/kg/hr IV Discontinue at end of PCI, or continue for up to 4 hr after procedure if needed Hold UFH 30 min before administration

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Table 9. Antithrombotic Dosing in ACS with or without PCI

	UFH	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
Classification	Indirect thrombin inhibitor	LMWH	Factor Xa inhibitor	Direct thrombin inhibitor
STEMI ± PPCI	Supplemental doses to target ACT[a] If GP IIb/IIIa, UFH 50–70 units/kg IVB If no GP IIb/IIIa, UFH 70–100 units/kg IVB	30 mg IVB, followed immediately by 1 mg/kg SC every 12 hr; do not exceed 100 mg on first two doses If > 75 yr, omit bolus; 0.75 mg/kg SC every 12 hr; do not exceed 75 mg on first two doses	2.5 mg IVB; then 2.5 mg SC daily	0.75 mg/kg IVB, 1.75 mg/kg/hr IV
Dose adjustments and CIs	Avoid if history of HIT	If CrCl < 30 mL/min/1.73 m^2, 1 mg/kg SC daily Avoid if history of HIT	CI if CrCl < 30 mL/min/1.73 m^2	Adjust infusion dose in severe renal dysfunction If CrCl < 30 mL/min/1.73 m^2, reduce infusion to 1 mg/kg/hr; if on hemodialysis, reduce infusion to 0.25 mg/kg/hr

[a]Target ACT is 250–300 s for HemoTec and I-Stat and 300–350 s for Hemochron without GP IIb/IIIa inhibitors and is 200–250 s in patients given concomitant GP IIb/IIIa inhibitors.

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Fibrinolytic Therapy

	≥65kg	<65kg
Alteplase (**accelerated regimen**) The maximum total dose of alteplase is 100mg.	**Step 1:** 15mg IV bolus	**Step 1**: 15mg IV bolus
	Step 2: 50mg IV infusion over 30 minutes	**Step 2:** 0.75mg/kg (Max 50mg) IV infusion over 30 minutes
	Step 3: 35mg IV infusion over 60 minutes	**Step 3:** 0.5mg/kg (Max 35mg) IV infusion over 60 minutes
Reteplase (r-PA, Retavase)	10 units IVP; repeat 10 units IV in 30 min	
Tenecteplase (TNK-t-PA, TNKase)	< 60 kg: 30 mg IVP; 60–69 kg: 35 mg IVP; 70–79 kg: 40 mg IVP; 80–89 kg: 45 mg IVP; > 90 kg: 50 mg IVP (~0.5 mg/kg)	

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